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EWS 1		Web Page URLs for STN Seminar Schedule - N. America
EWS 2	Apr 08	"Ask CAS" for self-help around the clock
EWS 3	Apr 09	BEILSTEIN: Reload and Implementation of a New Subject Area
EWS 4	Apr 09	ZDB will be removed from STN
EWS 5	Apr 19	US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
EWS 6	Apr 22	Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
EWS 7	Apr 22	BIOSIS Gene Names now available in TOXCENTER
EWS 8	Apr 22	Federal Research in Progress (FEDRIP) now available
EWS 9	Jun 03	New e-mail delivery for search results now available
EWS 10	Jun 10	MEDLINE Reload
EWS 11	Jun 10	PCTFULL has been reloaded
EWS 12	Jul 02	FOREGE no longer contains STANDARDS file segment
EWS 13	Jul 22	USAN to be reloaded July 28, 2002; saved answer sets no longer valid
EWS 14	Jul 29	Enhanced polymer searching in REGISTRY
EWS 15	Jul 30	NETFIRST to be removed from STN
EWS 16	Aug 08	CANCERLIT reload
EWS 17	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
EWS 18	Aug 08	NTIS has been reloaded and enhanced
EWS 19	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
EWS 20	Aug 19	IFIPAT, IFICDB, and IFIUDB have been reloaded
EWS 21	Aug 19	The MEDLINE file segment of TOXCENTER has been reloaded
EWS 22	Aug 26	Sequence searching in REGISTRY enhanced
EWS 23	Sep 03	JAPIO has been reloaded and enhanced
EWS 24	Sep 16	Experimental properties added to the REGISTRY file
EWS 25	Sep 16	CA Section Thesaurus available in CAPLUS and CA
EWS 26	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
EWS 27	Oct 21	EVENTLINE has been reloaded
EWS 28	Oct 24	BEILSTEIN adds new search fields
EWS 29	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
EWS 30	Oct 25	MEDLINE SDI run of October 8, 2002
EWS 31	Nov 18	DKILIT has been renamed APOLLIT
EWS 32	Nov 25	More calculated properties added to REGISTRY
EWS 33	Dec 02	TIBKAT will be removed from STN
EWS 34	Dec 04	CSA files on STN
EWS 35	Dec 17	PCTFULL now covers WP/PCT Applications from 1978 to date
EWS 36	Dec 17	TOXCENTER enhanced with additional content
EWS 37	Dec 17	Adis Clinical Trials Insight now available on STN
EWS 38	Dec 30	ISMEC no longer available
EWS 39	Jan 13	Indexing added to some pre-1967 records in CA/CAPLUS
EWS 40	Jan 21	NUTRACEUT offering one free connect hour in February 2003
EWS 41	Jan 21	PHARMAML offering one free connect hour in February 2003
EWS 42	Jan 29	Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC
EWS 43	Feb 13	CANCERLIT is no longer being updated
EWS 44	Feb 24	METADEX enhancements
EWS 45	Feb 24	PCTGEN now available on STN
EWS 46	Feb 24	TEMA now available on STN
EWS 47	Feb 26	NTIS now allows simultaneous left and right truncation
EWS 48	Feb 26	PCTFULL now contains images
EWS 49	Mar 04	SDI PACKAGE for monthly delivery of multifile SDI results

EWS EXPRESS January 6 CURRENT WINDOWS VERSION IS V6.01a,
CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
AND CURRENT DISCOVER FILE IS DATED 01 OCTOBER 2002

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EWS WWW       CAS World Wide Web Site (general information)

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LE COVERS 1907 - 5 Mar 2003  VOL 138 ISS 10
LE LAST UPDATED: 4 Mar 2003  (20030304/ED)

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ELP COMMANDS" at an arrow prompt (=>).

s liposomes (p) imexon
      34400 LIPOSOMES
         22 IMEXON
          1 LIPOSOMES (P) IMEXON

d 1 kwic

   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2003 ACS
   Drug delivery systems
      (liposomes; liposomal compns. comprising imexon
      derivs.)
```

d 1 bib ab

'ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS
2002:408506 CAPLUS
137:10970
Liposomal compositions comprising imexon derivatives
Lopez-Berestein, Gabriel; Remers, William A.; Hersh, Evan M.
Board of Regents, the University of Texas System, USA; Arizona Board of Regents, University of Arizona
PCT Int. Appl., 106 pp.
CODEN: PIXXD2
Patent
English
N.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002041871	A2	20020530	WO 2001-US43292	20011120
AU 2002016672	A5	20020603	AU 2002-16672	20011120
AI US 2000-721040	A1	20001121		
WO 2001-US43292	W	20011120		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

Disclosed are novel compns. comprising a lipid and imexon or a deriv. thereof. Also disclosed are liposomal compns. comprising imexon or deriv. thereof. Methods for administering pharmaceutically acceptable compns. comprising a lipid and imexon or a deriv. thereof for the treatment of diseases, such as cancer, are also disclosed herein. Thus, 2-cyanoaziridine-1-(N-methyl)carboxamide (I) was prepd. by the reaction of 2-cyanoaziridine with Me isocyanate. Antitumor activity of liposomal I was tested against a panel of tumor cells in culture.

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E COVERS 1907 - 5 Mar 2003 VOL 138 ISS 10
E LAST UPDATED: 4 Mar 2003 (20030304/ED)

his file contains CAS Registry Numbers for easy and accurate
ubstance identification.

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s imexon (p) lipid?
         22 IMEXON
     288161 LIPID?
          1 IMEXON (P) LIPID?

d 1

   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2003 ACS
   2002:408506  CAPLUS
   137:10970
   Liposomal compositions comprising imexon derivatives
   Lopez-Berestein, Gabriel; Remers, William A.; Hersh, Evan M.
   Board of Regents, the University of Texas System, USA; Arizona Board of
   Regents, University of Arizona
   PCT Int. Appl., 106 pp.
   CODEN: PIXXD2
   Patent
   English
N.CNT 1
   PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
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   WO 2002041871      A2   20020530       WO 2001-US43292  20011120
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            LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
            PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,
            UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
        RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
            CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
            BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
   AU 2002016672      A5   20020603       AU 2002-16672    20011120
AI US 2000-721040     A1   20001121
   WO 2001-US43292    W    20011120


s imexon (p) emulsion?
         22 IMEXON
     210578 EMULSION?
          0 IMEXON (P) EMULSION?

s imexon and phospholipid?
         22 IMEXON
     109542 PHOSPHOLIPID?
          2 IMEXON AND PHOSPHOLIPID?

d 1-2

   ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2003 ACS
   2002:408506  CAPLUS
   137:10970
   Liposomal compositions comprising imexon derivatives
   Lopez-Berestein, Gabriel; Remers, William A.; Hersh, Evan M.
   Board of Regents, the University of Texas System, USA; Arizona Board of
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   PCT Int. Appl., 106 pp.
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.CNT 1
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   WO 2002041871      A2   20020530       WO 2001-US43292  20011120
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            GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
            LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
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PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,
UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
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AU	2002016672	A5	20020603	AU 2002-16672	20011120
AI US	2000-721040	A1	20001121		
	WO 2001-US43292	W	20011120		

ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS
2002:95271 CAPLUS
136:395484
Molecular and cellular characterization of **imexon**-resistant
RPMI8226/I myeloma cells
Dvorakova, Katerina; Payne, Claire M.; Tome, Margaret E.; Briehl, Margaret
M.; Vasquez, Miguel A.; Waltmire, Caroline N.; Coon, Amy; Dorr, Robert T.
Arizona Cancer Center, University of Arizona, Tucson, AZ, 85724, USA
Molecular Cancer Therapeutics (2002), 1(3), 185-195
CODEN: MCTOCF; ISSN: 1535-7163
American Association for Cancer Research
Journal
English
.CNT 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

d 1-2 bib ab

ANSWER 1 OF 2 CAPLUS COPYRIGHT 2003 ACS
2002:408506 CAPLUS
137:10970
Liposomal compositions comprising **imexon** derivatives
Lopez-Berestein, Gabriel; Remers, William A.; Hersh, Evan M.
Board of Regents, the University of Texas System, USA; Arizona Board of
Regents, University of Arizona
PCT Int. Appl., 106 pp.
CODEN: PIXXD2
Patent
English
I.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002041871	A2	20020530	WO 2001-US43292	20011120

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
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BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU	2002016672	A5	20020603	AU 2002-16672	20011120
I US	2000-721040	A1	20001121		
	WO 2001-US43292	W	20011120		

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was prepd. by the reaction of 2-cyanoaziridine with Me isocyanate.
Antitumor activity of liposomal I was tested against a panel of tumor
cells in culture.

ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS
2002:95271 CAPLUS
136:395484
Molecular and cellular characterization of **imexon**-resistant

RPMI8226/I myeloma cells
Dvorakova, Katerina; Payne, Claire M.; Tome, Margaret E.; Briehl, Margaret M.; Vasquez, Miguel A.; Waltmire, Caroline N.; Coon, Amy; Dorr, Robert T.
Arizona Cancer Center, University of Arizona, Tucson, AZ, 85724, USA
Molecular Cancer Therapeutics (2002), 1(3), 185-195
CODEN: MCTOCF; ISSN: 1535-7163
American Association for Cancer Research
Journal
English
Imexon is an aziridine-contg. iminopyrrolidone with selective growth-inhibitory potency for multiple myeloma. Our previous research indicates that **imexon** induces mitochondrial alterations, oxidative stress, and apoptosis. This drug represents an interesting model drug with a nonmyelosuppressive profile to study the basic mechanisms leading to antitumor activity and resistance. The major purpose of this study was to characterize an **imexon**-resistant RPMI8226/I cell line that was developed from RPMI8226 cells by continuous exposure to **imexon**. No significant differences were obsd. in the sensitivity to several cytotoxic drugs, including mitoxantrone, mitomycin C, melphalan, methotrexate, cytarabine, cisplatin, vincristine, and paclitaxel, in the **imexon**-resistant cells. However, RPMI8226/I cells were cross-resistant to arsenic trioxide, doxorubicin, fluorouracil, etoposide, irinotecan, and esp. IFN-.alpha.. The data from DNA microarray and Western blot analyses indicated that the levels of antiapoptotic proteins Bcl-2 and thioredoxin-2, which reside mainly in the mitochondria, are increased in RPMI8226/I cells. In addn., increased levels of lung resistance protein were detected in **imexon** -resistant cells. Expression of P-glycoprotein was not detected in RPMI8226/I cells. No loss of mitochondrial membrane potential or increase in the levels of reactive oxygen species was obsd. in RPMI8226/I cells after exposure to **imexon**; however, the levels of glutathione are increased in the RPMI8226/I cells. TEM revealed significant changes in the mitochondrial morphol. of RPMI8226/I cells, whereas no ultrastructural changes were obsd. in other cellular compartments. **Imexon** -resistant RPMI8226/I myeloma cells appear to have a unique mechanism of resistance that is assocd. with morphol. alterations of mitochondria, increased protection against oxidative stress, elevated levels of glutathione, and enhanced expression of antiapoptotic mitochondrial proteins.
.CNT 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

imexon (p) micelle?
22 IMEXON
49009 MICELLE?
1 IMEXON (P) MICELLE?

d 1

ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS
2002:408506 CAPLUS
137:10970
Liposomal compositions comprising imexon derivatives
Lopez-Berestein, Gabriel; Remers, William A.; Hersh, Evan M.
Board of Regents, the University of Texas System, USA; Arizona Board of Regents, University of Arizona
PCT Int. Appl., 106 pp.
CODEN: PIXXD2
Patent
English
.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002041871	A2	20020530	WO 2001-US43292	20011120

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,
UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU	2002016672	A5	20020603	AU 2002-16672	20011120
AI US	2000-721040	A1	20001121		
	WO 2001-US43292	W	20011120		

s imexon
22 IMEXON

d 1-22 bib ab

ANSWER 1 OF 22 CAPLUS COPYRIGHT 2003 ACS
2002:875617 CAPLUS
Imexon activates an intrinsic apoptosis pathway in RPMI8226 myeloma cells
Dvorakova, Katerina; Payne, Claire M.; Landowski, Terry H.; Tome, Margaret E.; Halperin, Daniel S.; Dorr, Robert T.
Dep. Microbiol. and Immunology, Univ. Arizona, Tucson, AZ, 85724, USA
Anti-Cancer Drugs (2002), 13(10), 1031-1042
CODEN: ANTDEV; ISSN: 0959-4973
Lippincott Williams & Wilkins
Journal
English
Imexon is a new antitumor agent with high activity in multiple myeloma. This drug induces apoptosis, oxidative stress and mitochondrial alterations. However, it was unknown whether **imexon** activates an intrinsic apoptotic pathway that is assocd. with activation of caspase-9 or an extrinsic pathway that is induced by receptor-mediated signals such as Fas ligand characterized by caspase-8 activation. In addn., we wanted to investigate the effect of **imexon** on Bcl-2 family proteins. In RPMI8226 myeloma cells, **imexon** activated caspase-9 and -3 in a time- and concn.-dependent manner. In contrast, cleavage of procaspase-8 was obsd. late and only after exposure to very high concns. of **imexon**. Confocal microscopy confirmed that caspase-3 is also activated after treatment with **imexon**. High **imexon** concns. activated caspase-3 and -9 at 12 h, while caspase-8 activation occurred only at 48 h. **Imexon** cytotoxicity was unchanged in three RPMI8226 cell lines with different levels (low, medium and high) of FAS expression. Similarly, the levels of Bcl-2, Bax and Bcl-x were unchanged in **imexon**-treated cells. However, Bcl-x was translocated to the mitochondria. These data suggest that **imexon**-induced oxidn. activates the intrinsic or mitochondrial pathway of apoptosis, involving cytochrome release and activation of caspase-9 and -3.L L.
CNT 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 2 OF 22 CAPLUS COPYRIGHT 2003 ACS
2002:845603 CAPLUS
137:337772
Preparation of 2-cyanoaziridine-1-carboxamides by reaction of aziridines with isocyanates followed by treatment with nucleophiles.
Remers, William; Iyengar, Bashyam
The Arizona Board of Regents, USA
U.S., 5 pp.
CODEN: USXXAM
Patent
English
.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6476236	B1	20021105	US 2001-995265	20011126
I US 2001-995265		20011126		

CASREACT 137:337772; MARPAT 137:337772

Title compds. (I; R1-R3 = H, alkyl; R4 = cyano, carboxamide, carboxylate ester) were prepd. by reaction of the corresponding unacylated aziridines with R5NCO (R5 = COR6; R6 = haloalkyl) followed by treatment of the intermediate with a nucleophile. In addn., the invention provides a process for producing 4-imino-1,3-diazabicyclo[3.1.0]-hexan-2-ones (II; variables as above) from I. Thus, 2-cyanoaziridine in PhMe was added over 1 h to Cl3CCONCO in PhMe at -10.degree. followed by stirring for addnl. 1 h storage overnight at 5.degree. to give 2-cyanoaziridine-1-[N-(trichloroacetyl)]carboxamide. The latter was stirred with NH3 in MeOH at 0.degree. for 1.5 h to give 2-cyanoaziridine-2-carboxamide.

.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 3 OF 22 CAPLUS COPYRIGHT 2003 ACS
2002:408506 CAPLUS
137:10970
Liposomal compositions comprising **imexon** derivatives
Lopez-Berestein, Gabriel; Remers, William A.; Hersh, Evan M.
Board of Regents, the University of Texas System, USA; Arizona Board of Regents, University of Arizona
PCT Int. Appl., 106 pp.
CODEN: PIXXD2
Patent
English

N.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002041871	A2	20020530	WO 2001-US43292	20011120
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002016672	A5	20020603	AU 2002-16672	20011120
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2002:95271 CAPLUS
136:395484
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Dvorakova, Katerina; Payne, Claire M.; Tome, Margaret E.; Briehl, Margaret M.; Vasquez, Miguel A.; Waltmire, Caroline N.; Coon, Amy; Dorr, Robert T.
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Molecular Cancer Therapeutics (2002), 1(3), 185-195
CODEN: MCTOCF; ISSN: 1535-7163
American Association for Cancer Research
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English
Imexon is an aziridine-contg. iminopyrrolidone with selective growth-inhibitory potency for multiple myeloma. Our previous research indicates that **imexon** induces mitochondrial alterations, oxidative stress, and apoptosis. This drug represents an interesting model drug with a nonmyelosuppressive profile to study the basic mechanisms leading to antitumor activity and resistance. The major

purpose of this study was to characterize an **imexon**-resistant RPMI8226/I cell line that was developed from RPMI8226 cells by continuous exposure to **imexon**. No significant differences were obsd. in the sensitivity to several cytotoxic drugs, including mitoxantrone, mitomycin C, melphalan, methotrexate, cytarabine, cisplatin, vincristine, and paclitaxel, in the **imexon**-resistant cells. However, RPMI8226/I cells were cross-resistant to arsenic trioxide, doxorubicin, fluorouracil, etoposide, irinotecan, and esp. IFN-.alpha.. The data from DNA microarray and Western blot analyses indicated that the levels of antiapoptotic proteins Bcl-2 and thioredoxin-2, which reside mainly in the mitochondria, are increased in RPMI8226/I cells. In addn., increased levels of lung resistance protein were detected in **imexon** -resistant cells. Expression of P-glycoprotein was not detected in RPMI8226/I cells. No loss of mitochondrial membrane potential or increase in the levels of reactive oxygen species was obsd. in RPMI8226/I cells after exposure to **imexon**; however, the levels of glutathione are increased in the RPMI8226/I cells. TEM revealed significant changes in the mitochondrial morphol. of RPMI8226/I cells, whereas no ultrastructural changes were obsd. in other cellular compartments. **Imexon** -resistant RPMI8226/I myeloma cells appear to have a unique mechanism of resistance that is assocd. with morphol. alterations of mitochondria, increased protection against oxidative stress, elevated levels of glutathione, and enhanced expression of antiapoptotic mitochondrial proteins.

.CNT 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 5 OF 22 CAPLUS COPYRIGHT 2003 ACS
2001:417780 CAPLUS
135:220890
Induction of mitochondrial changes in myeloma cells by **imexon**
Dvorakova, Katerina; Waltmire, Caroline N.; Payne, Claire M.; Tome, Margaret E.; Briehl, Margaret M.; Dorr, Robert T.
Arizona Cancer Center, Department of Microbiology and Immunology, University of Arizona, Tucson, AZ, USA
Blood (2001), 97(11), 3544-3551
CODEN: BLOOAW; ISSN: 0006-4971
American Society of Hematology
Journal
English
Imexon is a cyanoaziridine deriv. that has antitumor activity in multiple myeloma. Previous studies have shown that **imexon** induces oxidative stress and apoptosis in the RPMI 8226 myeloma cell line. This study reports that **imexon** has cytotoxic activity in other malignant cell lines including NCI-H929 myeloma cells and NB-4 acute promyelocytic leukemia cells, whereas normal lymphocytes and U266 myeloma cells are substantially less sensitive. Flow cytometric expts. have shown that **imexon** treatment is assocd. with the formation of reactive oxygen species (ROS) and the loss of mitochondrial membrane potential (.DELTA..psi.m) in **imexon**-sensitive myeloma cell lines and NB-4 cells. In contrast, redn. of .DELTA..psi.m and increased levels of ROS were not obsd. in **imexon**-resistant U266 cells. Treatment of **imexon**-sensitive RPMI 8226 cells with the antioxidant N-acetyl-L-cysteine (NAC) protects cells against these effects of **imexon**. Mitochondrial swelling was obsd. by electron microscopy in RPMI 8226 myeloma cells treated with 180 .mu.M **imexon** as early as 4 h. Damage to mitochondrial DNA was detected by a semiquant. polymerase chain reaction assay in **imexon**-treated RPMI 8226 cells; however, nuclear DNA was not affected. Finally, partial protection of RPMI 8226 cells against the **imexon** effects was achieved by treatment with thenoyltrifluoroacetone, an inhibitor of superoxide prodn. at mitochondrial complex II. These changes are consistent with mitochondrial oxidn. and apoptotic signaling as mediators of the growth inhibitory effects of **imexon**. Interestingly, oxidative damage and decrease of .DELTA..psi.m induced by **imexon** highly correlates with sensitivity to **imexon** in several myeloma cell lines and an acute promyelocytic leukemia cell line.

CNT 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 6 OF 22 CAPLUS COPYRIGHT 2003 ACS
2001:264704 CAPLUS
135:40605
Mechanisms of **imexon** action in human myeloma cells
Dvorakova, Katerina
Univ. of Arizona, Tucson, AZ, USA
(2000) 151 pp. Avail.: UMI, Order No. DA9972072
From: Diss. Abstr. Int., B 2000, 61(5), 2484
Dissertation
English
Unavailable

ANSWER 7 OF 22 CAPLUS COPYRIGHT 2003 ACS
2000:531351 CAPLUS
133:246877
Induction of oxidative stress and apoptosis in myeloma cells by the aziridine-containing agent **imexon**
Dvorakova, K.; Payne, C. M.; Tome, M. E.; Briehl, M. M.; McClure, T.; Dorr, R. T.
Arizona Cancer Center, The University of Arizona, Tucson, AZ, 85724, USA
Biochemical Pharmacology (2000), 60(6), 749-758
CODEN: BCPCA6; ISSN: 0006-2952
Elsevier Science Inc.
Journal
English
Imexon is an iminopyrrolidone deriv. that has selective antitumor activity in multiple myeloma. The exact mechanism of **imexon** action is unknown. In human 8226 myeloma cells, the cytotoxicity of **imexon** was schedule-dependent, and long exposures (.gtoreq.48 h) to low concns. of **imexon** were most effective at inducing cytotoxicity. Our data suggest that **imexon** does not affect DNA, but it can alkylate thiols by binding to the sulfhydryl group. We have also demonstrated by HPLC studies that in human 8226 myeloma cells, **imexon** depletes cellular stores of cysteine and glutathione. Oxidative stress in 8226 cells exposed to **imexon** was detected by immunohistochem. staining with a monoclonal antibody to 8-hydroxydeoxyguanosine (8-OHdG), followed by confocal microscopy. These images showed increased levels of 8-OHdG in the cytoplasm of cells treated with different concns. of **imexon** at 8, 16, and 48 h. Interestingly, 8-OHdG staining was not obsd. in the nuclei of **imexon**-treated cells, in contrast to the diffuse staining seen with t-Bu hydroperoxide. Myeloma cells exposed to **imexon** showed classic morphol. features of apoptosis upon electron microscopy, and increased levels of phosphatidylserine exposure, detected as Annexin-V binding, on the cell surface. To prevent depletion of thiols, 8226 myeloma cells exposed to **imexon** were treated with N-acetylcysteine (NAC). Simultaneous, as well as sequential, treatment with NAC before **imexon** exposure resulted in protection of myeloma cells against **imexon**-induced cytotoxicity. Conversely, the glutathione synthesis inhibitor buthionine sulfoximine increased **imexon** cytotoxicity. These data suggest that **imexon** perturbs cellular thiols and induces oxidative stress leading to apoptosis in human myeloma cells.
CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 8 OF 22 CAPLUS COPYRIGHT 2003 ACS
1999:401696 CAPLUS
131:43589
Diagnostics and therapeutics for transmissible spongiform encephalopathy and methods for the manufacture of non-infective blood products and tissue derived products
Aguzzi, Adriano; Klein, Michael A.; Raeber, Alex; Weissmann, Charles; Zinkernagel, Rolf
University of Zurich, Switz.
PCT Int. Appl., 162 pp.
CODEN: PIXXD2
Patent

English
N.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9930738	A2	19990624	WO 1998-EP8271	19981216
WO 9930738	A3	19991021		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 931551	A1	19990728	EP 1997-122186	19971216
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
EP 1214943	A1	20020619	EP 2001-127424	19971216
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
EP 1215497	A1	20020619	EP 2001-127425	19971216
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
AU 9926131	A1	19990705	AU 1999-26131	19981216
EP 1044020	A2	20001018	EP 1998-966899	19981216
R: AT, BE, CH, DE, ES, FR, GB, IT, LI, NL				
JP 2002508335	T2	20020319	JP 2000-538717	19981216
AI EP 1997-122186	A	19971216		
WO 1998-EP8271	W	19981216		

B-cells have been identified as being the crucial carriers of infectivity in the spread of transmissible spongiform encephalopathy within an infected organism. In a second step, B-cells may infect further components of the immune system, e.g. T-cells. Accordingly, the present invention provides B-cell and T-cell specific ligands for the use in diagnostics and therapeutics for transmissible spongiform encephalopathy and provides methods for the manuf. of non-infective blood products and tissue derived products. Thus, the present invention provides medicaments comprising B-cell and/or T-cell depletants, for the treatment of pathologies where the depletion of B-cells and/or T-cells, and more particularly of tse-infected B-cells and/or T-cells is therapeutically effective. The B cell depletant includes anti-B cell antibody such as rituximab and B220 or chem. compd. such as **imexon** and ciamexone; the T cell depletant includes anti-T cell antibody or chem. compd. such as cyclosporin A; and B/T cell depletant includes combination of cyclophosphamide and dexamethasone.

ANSWER 9 OF 22 CAPLUS COPYRIGHT 2003 ACS
1999:59396 CAPLUS
130:261455
Novel Antitumor 2-Cyanoaziridine-1-carboxamides
Iyengar, Bhashyam S.; Dorr, Robert T.; Alberts, David S.; Hersh, Evan M.; Salmon, Sydney E.; Remers, William A.
Department of Pharmacology and Toxicology and Arizona Cancer Center, University of Arizona, Tucson, AZ, 85721, USA
Journal of Medicinal Chemistry (1999), 42(3), 510-514
CODEN: JMCMAR; ISSN: 0022-2623
American Chemical Society
Journal
English
A set of 20 2-cyanoaziridine-1-carboxamides was synthesized from 2-cyanoaziridine and appropriate isocyanates. These compds. were active against a variety of solid and hematol. tumor cells in culture, including strains resistant to doxorubicin and mitoxantrone. Their potencies in these assays correlated with the lipophilicity of substituents. The N-Ph deriv. was more potent and equally effective to **imexon**, a cyclized 2-cyanoaziridine-1-carboxamide of clin. interest, against cloned fresh human tumors.
CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 10 OF 22 CAPLUS COPYRIGHT 2003 ACS
1996:68824 CAPLUS
124:135035
Preclinical pharmacokinetics and antitumor activity of **imexon**
Dorr, Robert T.; Liddil, James D.; Klein, Mary Kay; Hersh, Evan M.
Arizona Cancer Center, College Medicine, Tucson, AZ, 85724, USA
Investigational New Drugs (1995), 13(2), 113-16
CODEN: INNDDK; ISSN: 0167-6997
Kluwer
Journal
English
Imexon is an aziridine compd. originally studied for immune-enhancing effects on lymphocytes. The drug was well-tolerated in humans and was shown to be active in a variety of animal tumor models. Recently, **imexon** has demonstrated antitumor activity in human multiple myeloma cell lines in vitro. The pharmacokinetics of the compd. using a normal phase HPLC assay were studied in normal mice and in dogs with mast cell tumors. Doses of 100 mg/kg given i.p. produced peak plasma levels over 100 .mu.g/mL in mice and the drug was rapidly eliminated with half lives of 8 min (.alpha. phase) and 29 min (.beta. phase). Only 20% of an oral **imexon** dose was absorbed in the mouse. In dogs, the .alpha. and .beta. phase half lives ranged from 18-26 min and 91-110 min, resp. Peak levels over 100 .mu.g/mL were obtained following i.v. doses of 12.5 mg/kg and 25 mg/kg. **Imexon** was active in mice bearing either P-388 or L-1210 leukemia, but not in mice with B-16 melanoma. These results suggest that cytotoxic drug concns. can be obtained in vivo and that **imexon** is active in lymphoproliferative tumors.

ANSWER 11 OF 22 CAPLUS COPYRIGHT 2003 ACS
1994:692072 CAPLUS
121:292072
Antiviral and immunomodulating inhibitors of experimentally-induced Punta Toro virus infections
Sidwell, Robert W.; Huffman, John H.; Barnard, Dale L.; Smee, Donald F.; Warren, Reed P.; Chirigos, Michael A.; Kende, Meir; Huggins, John
Institute for Antiviral Research, Utah State University, Logan, UT, 84322-5600, USA
Antiviral Research (1994), 25(2), 105-22
CODEN: ARSRDR; ISSN: 0166-3542
Elsevier
Journal
English
A major component of a US Army Medical Research and Development Command-supported program to discover and develop new drugs for the treatment of Rift Valley fever, sandfly fever, and Crimean-Congo hemorrhagic fever has been to study candidate test materials against hepatotropic infections of C57BL/6 mice induced by the related but less biohazardous Punta Toro virus (PTV). The effects of 75 compds., some of which were considered immunomodulators in their primary mechanism of activity, were studied in the PTV infection model. Of these, ribavirin, ribamidine, ribavirin 2',3',5'-triacetate, tiazofurin, tiazofurin-5'-monophosphate, tiazofurin-2',3',5'-triacetate, selenazofurin, pyrazofurin, 3-deazaguanine, and 3-deazaguanosine were considered significantly inhibitory, acting against the infection by a direct antiviral (non-immunomodulatory) fashion. These compds. had therapeutic indexes (TI) ranging from .gtoreq.5 to 65, using increased survivors as the evaluation parameter. Immunomodulators considered significantly inhibitory to this infection were poly (ICLC), ampligen, human recombinant interferon-.alpha.-A/D, MVE-1, MVE-2, AM-3, AM-5, mannozym, bropirimine, CL246,738, phenyleneamine, and 7-thia-8-oxoguanosine. Utilizing increased survivor nos. as measure of activity, these inhibitors had TI ranging from .gtoreq.16 to 1000. Other antiviral effects exerted by the active compds. included redn. of hepatic icterus, lowered serum glutamic oxaloacetic and pyruvic acid transaminases, and inhibition of recoverable serum and liver virus titers. The active immunomodulators were significantly effective when therapy was initiated as late as 48 h after virus inoculation, at a time when clin. signs of the PTV disease were being manifested in the animal.

ANSWER 12 OF 22 CAPLUS COPYRIGHT 2003 ACS
1993:573802 CAPLUS
119:173802
Immunomodulator effects on the Friend virus infection in genetically defined mice
Sidwell, R. W.; Morrey, J. D.; Okleberry, K. M.; Burger, R. A.; Warren, R. P.
Inst. Antiviral Res., Utah State Univ., Logan, UT, 84322-5600, USA
Annals of the New York Academy of Sciences (1993), 685(Immunomodulating Drugs), 432-46
CODEN: ANYAA9; ISSN: 0077-8923
Journal
English
The disease induced by the Friend virus complex (FV) in F1 hybrid mice contg. the Rff-3r/s genotype in the presence of H-2a/a was used to evaluate a variety of immunomodulating substances. In these genetically defined mice, the FV disease results in splenomegaly, early prodn. of high titers of cell-assocd. and plasma virus, high; levels of splenic viral RNA, increased hematocrit, and eventual death. As the disease progresses, reduced levels of infectious virus correlate with development of specific antibody; redn. in T cell populations, increase in B cells, and decrease in T-cell function also occur. The following immunomodulators were evaluated, listed in the order of their ability to inhibit the FV disease: **imexon** > MVE-2 > human recombinant IFN-a A/D > AS101 > ampligen > AM-3 = > ImuVert > bropirimine. In fact, bropirimine, used with certain treatment regimens, appeared to enhance the FV disease. These data suggest that certain immunomodulators may have potential value in the treatment of HIV disease, but also indicate that caution should by exercised in their clin. use.

ANSWER 13 OF 22 CAPLUS COPYRIGHT 2003 ACS
1992:584412 CAPLUS
117:184412
Antiproliferative and antitumor activity of the 2-cyanoaziridine compound **imexon** on tumor cell lines and fresh tumor cells in vitro
Hersh, Evan M.; Gschwind, Charles R.; Taylor, Charles W.; Dorr, Robert T.; Taetle, Raymond; Salmon, Sydney E.
Sect. Hematol. Oncol., Arizona Cancer Cent., Tucson, AZ, 85724, USA
Journal of the National Cancer Institute (1992), 84(16), 1238-44
CODEN: JNCIEQ; ISSN: 0027-8874
Journal
English
The concn. of **imexon** that caused 50% inhibition of cell growth was <10 .mu.g/mL for mitogen-stimulated lymphocytes and was 3-10 .mu.g/mL for B-cell lymphomas and both multidrug-resistant and -sensitive myeloma cell lines. **Imexon** inhibited 4 of 7 fresh lymphoma and 11 of 16 fresh myeloma biopsy specimens to <40% of control growth. A 1-h exposure of lymphoma cells to 50-100 .mu.g **imexon**/mL, followed by removal of drug and continuing culture, resulted in >95% inhibition during the next 48-72 h. **Imexon** selectively inhibited protein formation during the 1st 24-48 h of exposure of lymphoma and myeloma cells. Cells exposed to inhibitory concns. of **imexon** were blocked in cell cycle progression. **Imexon** may be a useful agent in the treatment of malignant diseases, exp. lymphoid malignancies.

ANSWER 14 OF 22 CAPLUS COPYRIGHT 2003 ACS
1992:524079 CAPLUS
117:124079
Treatment of the murine, retrovirus-induced lymphoproliferative immunodeficiency disease (LP-BM5) in C57BL/10 mice with the immunomodulator **imexon**
Funk, Carole Y.; Eisman, Julia; Hersh, Evan M.
Sect. Hematol. Oncol., Arizona Cancer Cent., Tucson, AZ, 85724, USA
AIDS Research and Human Retroviruses (1992), 8(5), 633-8
CODEN: ARHRE7; ISSN: 0889-2229
Journal
English
Imexon (4-imino-1,3-diazabicyclo-(3.1.0)-hexan-2-one) a

cyanoaziridine compd. was studied in the treatment of the murine retrovirus-induced immunodeficiency disease model of AIDS (LP-BM5, MAIDS). **Imexon**, in dose-dependent fashion, partially prevented the development of hypergammaglobulinemia and splenomegaly, and partially prevented the decline in the phytohemagglutinin-induced proliferative response of spleen lymphocytes when started 1 or 15 days after virus inoculation. There was a statistically significant redn. in these disease-assocd. manifestations. When animals were treated starting 78 or 92 days after virus inoculation, lymphadenopathy was completely abrogated and survival was significantly prolonged in a dose-responsive manner. Since **imexon** and other cyanoaziridine compds. have been safely administered to humans, the authors suggest that this class of compds. be further investigated in both large animal models of HIV infection and in patients with HIV-induced disease.

ANSWER 15 OF 22 CAPLUS COPYRIGHT 2003 ACS
1992:247956 CAPLUS
116:247956
Imexon and biological response modifiers in murine models of AIDS
Chirigos, Michael A.; Ussery, Michael A.; Black, Paul L.
U. S. Army Med. Res. Inst. Infect. Dis., Frederick, MD, 21702, USA
International Journal of Immunopharmacology (1991), 13(Suppl. 1), 33-41
CODEN: IJIMDS; ISSN: 0192-0561
Journal
English
The Rauscher murine leukemia retrovirus system provides an in vivo model of the human acquired immune deficiency syndrome for testing the ability of antiviral agents and biol. response modifiers (BRM) to suppress viremia and retroviral disease. In the present report the authors examd. three agents in the Rauscher retrovirus model: **imexon**, Ampligen and poly[I,C]-LC. **Imexon** reduced splenomegaly, viremia, and serum reverse transcriptase levels even when treatment was not initiated until 7 days after virus infection. **Imexon** also significantly prolonged the survival of infected mice. Thus it proved to be an effective antiviral agent in this system, although **imexon** did not completely eliminate retroviral infection in treated mice. Poly[I,C]-LC and Ampligen had immunomodulatory effects. Both of these BRM augmented the cytolytic activity of splenic natural killer (NK) cells in infected animals when treatment was initiated 24 h after infection. Poly[I,C]-LC had antiretroviral activity when administered on this schedule. In order to examine the role of NK cell augmentation in the antiviral activity of poly[I,C]-LC, the authors attempted to deplete NK activity by treatment with rabbit antibody to asialo-GM1, a ganglioside on the surface of murine NK cells. Combined treatment of infected mice with poly[I,C]-LC and anti-asialo-GM1 decreased the antiviral activity of poly[I,C]-LC. This finding suggests that NK cells may be involved in the antiviral effect of this BRM.

ANSWER 16 OF 22 CAPLUS COPYRIGHT 2003 ACS
1992:187557 CAPLUS
116:187557
Elucidation of mode of retroviral-inhibitory effects of **imexon** through use of immune competent and severe combined immune deficiency (SCID) mice
Morrey, John D.; Mead, Jan R.; Warren, Reed P.; Okleberry, Kevin M.; Burger, Roger A.; Sidwell, Robert W.
AIDS Res. Program, Utah State Univ., Logan, UT, 84322-5600, USA
Antiviral Research (1992), 17(3), 223-33
CODEN: ARSRDR; ISSN: 0166-3542
Journal
English
Mice infected with various tumor retroviruses have been used as models for evaluating therapeutic substances for the treatment of some cancers, and more recently, for human immunodeficiency virus (HIV) infection, the causative agent of acquired immune deficiency syndrome (AIDS). Consequently, there is a need to det. the ability of biol. response modifiers (BRMs) to specifically reduce virus-infected cells, as compared to their non-specific antiproliferative effects. To address this need, a

BRM, **imexon**, was evaluated in this study using three strains of mice having different Friend virus (FV)-specific immunol. capabilities. The first strain, (B10.A .times. A/WySn)F1, was genetically capable of producing FV-specific neutralization and cytotoxic antibodies, the second, Balb/c, was not, and the third, SCID mice, lacked functional T and B cell immunity. **Imexon** treatment reduced virally-induced splenomegaly in all 3 strains; however, the concn. of splenic viral infectious centers (IC) were not affected. Since **imexon** was efficacious in reducing splenomegaly in SCID mice, the mode of action was concluded to not require functional T or B cell immunity. The observation that **imexon** did not affect splenic IC titers also suggested that **imexon** did not specifically eliminate virally infected cells, but may have functioned by other mechanisms. This study also demonstrated the use of various mouse strains as a strategy for delineating the modes of action of BRMs against murine retroviral infections.

ANSWER 17 OF 22 CAPLUS COPYRIGHT 2003 ACS
1991:220817 CAPLUS
114:220817
Effect of **imexon** treatment on Friend virus complex infection using genetically defined mice as a model for HIV-1 infection
Morrey, John D.; Warren, Reed P.; Okleberry, Kevin M.; Burger, Roger A.; Chirigos, Michael A.; Sidwell, Robert W.
AIDS Res. Program, Utah State Univ., Logan, UT, 84322-5600, USA
Antiviral Research (1991), 15(1), 51-65
CODEN: ARSRDR; ISSN: 0166-3542
Journal
English
Imexon was moderately effective in the treatment of a retroviral infection in a genetically defined murine model. The animal model consisted of a Friend virus complex (FV) infection in a hybrid mouse strain, (B 10.A .times. A/WySn)F1 which has similarities with acquired immune deficiency syndrome (AIDS). I.p. **imexon**, initiated 1 or 3 days after FV inoculation and continued through 13 days after inoculation, reduced splenomegaly, splenic cell-free virus titers and viral RNA. Viral infectious centers/106 splenocytes and FV titers in the plasma were reduced, though not significantly. The effect of **imexon** on survival was not significant, which suggested that the antiviral effects were only transiently. Phytohemagglutinin-induced blastogenesis and the percentage of total T cells, T helper cells and T suppressor/cytotoxic cells in the spleens were increased, and the percentage of B cells decreased, by **imexon** treatment of both FV-infected and uninfected mice. Splenic natural killer cell activity and interleukin-1 prodn. were not markedly affected. Virus-specific neutralizing antibody developed in both **imexon**- and placebo-treated FV-infected mice, although titers were lower in the **imexon**-treated animals.

ANSWER 18 OF 22 CAPLUS COPYRIGHT 2003 ACS
1990:490967 CAPLUS
113:90967
Antiviral efficacy of **imexon** in the Rauscher murine retrovirus AIDS model
Chirigos, Michael A.; Ussery, Michael A.; Rankin, James T., Jr.; Herrmann, Dieter; Bicker, Uwe; Black, Paul L.
South Res. Inst., U. S. Army Med. Res. Inst. Infect. Dis., Ft. Detrick, MD, 21701, USA
Immunopharmacology and Immunotoxicology (1990), 12(1), 1-21
CODEN: IITOEF; ISSN: 0892-3973
Journal
English
The antiviral effects of **imexon** (I) were studied in BALB/c mice at different stages of infection with erythrotropic Ranscher murine leukemia virus (RMLV). AZT and ribavirin were used as pos. internal controls. The treatment with I (90 and 120 mg/kg) led to a suppression of splenomegaly by .gtoreq.50% as well as a decrease in viremia and serum reverse transcriptase (RT) levels. No differences were noted whether therapy was initiated one day prior to or on the same day of the RMLV inoculation. The drug was very effective in suppressing splenomegaly,

viremia, and RT when mice were sacrificed 14 days following treatment. However, there was a progressive decrease in body wt. assocd. with the higher concns. of I (10 and 18% decrease at the 170 and 220 mg/kg of I, resp.). Continuous treatment with 110 and 170 mg/kg for 20 days showed that I maintained its therapeutic effectiveness.

ANSWER 19 OF 22 CAPLUS COPYRIGHT 2003 ACS
1990:191949 CAPLUS
112:191949
Use of **imexon** as an immunosuppressive agent
Herrmann, Dieter; Haag, Rainer; Bosies, Elmar; Bicker, Uwe; Kampe, Wolfgang
Boehringer Mannheim G.m.b.H., Germany
Eur. Pat. Appl., 9 pp.
CODEN: EPXXDW
Patent
German

N.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 352652	A2	19900131	EP 1989-113425	19890721
EP 352652	A3	19910904		
EP 352652	B1	19950125		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
DE 3825667	A1	19900315	DE 1988-3825667	19880728
DE 3825667	C2	19910627		
DE 3844655	A1	19900517	DE 1988-3844655	19880728
DE 3844655	C2	19920730		
DE 3844839	C2	19940609	DE 1988-3844839	19880728
DK 8903633	A	19900129	DK 1989-3633	19890721
AU 8938877	A1	19900201	AU 1989-38877	19890724
AU 619027	B2	19920116		
CA 1333771	A1	19950103	CA 1989-606620	19890725
ZA 8905710	A	19900425	ZA 1989-5710	19890727
HU 52378	A2	19900728	HU 1989-3821	19890727
HU 206827	B	19930128		
IL 91138	A1	19941021	IL 1989-91138	19890727
JP 02088521	A2	19900328	JP 1989-194417	19890728
JP 2848634	B2	19990120		
US 5369119	A	19941129	US 1993-26210	19930302

AI DE 1988-3825667 19880728
DE 1988-3844655 19880728
US 1989-385920 19890727
US 1990-617301 19901120
US 1991-759204 19910911

Imexon is an immunosuppressant which selectively suppresses B-lymphocyte activation and can be used in the treatment of B-cell or plasma cell leukemias or neoplasias. Thus, **imexon** inhibited the proliferation of stimulated human B-lymphocytes in vitro and inhibited the growth of methylcholanthrene-induced fibrosarcoma cells. It was also active against autoimmune diseases and infection with Rauscher leukemia virus.

ANSWER 20 OF 22 CAPLUS COPYRIGHT 2003 ACS
1978:164124 CAPLUS
88:164124
Experimental investigations on increased resistance to Candida albicans and Staphylococcus aureus Smith infections following 4-imino-1,4-diazobicyclo[3.1.0]hexane-2-one BM 06.002 (prop. INN **imexon**) treatment in mice
Ziegler, A. E.; Bicker, U.; Hebold, G.
Dep. Immunostimul., Boehringer Mannheim G.m.b.H., Mannheim, Fed. Rep. Ger.
Experimentelle Pathologie (1967-1980) (1977), 14(6), 321-7
CODEN: EXPTAX; ISSN: 0014-4908
Journal
English
BM 06.002 (I) [59643-91-3] increased the resistance of mice to exptl. induced chronic infection with C. albicans. Furthermore, I led to increased resistance in the case of exptl. induced infection with S.

aureus when a subtherapeutic dose of sulfadiazine was applied. In mice immunosuppressively pretreated with hydrocortisone, I initiated the restoration of the immune response.

ANSWER 21 OF 22 CAPLUS COPYRIGHT 2003 ACS
1978:99172 CAPLUS
88:99172
Experimental studies on the stimulation of cell-mediated immunoreactivity using 4-imino-1,3-diazabicyclo(3.1.0)hexan-2-one (BM 06.002, prop. INN **Imexon**)
Bicker, U.; Hebold, G.
Abt. Immunstimulation, Boehringer Mannheim G.m.b.H., Mannheim, Fed. Rep. Ger.
Oesterreichische Zeitschrift fuer Onkologie (1977), 4(2-3), 55-6
CODEN: OZOKAN; ISSN: 0377-2004
Journal
German
BM 06002 (**Imexon**) (I) [59643-91-3] amplified cell-mediated immunoreactivity in mice, as measured by the increase in the delayed-type hypersensitivity reaction (paw edema) to a booster shot of sheep erythrocyte. Doses of 2.5 and 25 mg/kg (i.v., on days, 0, 1, and 2 of the 1st immunization) were more effective than a dose of 250 mg/kg, and the clearest response was at 24 h after the booster immunization. An increase in both T-cell and macrophage function may be the mechanism of I action.

ANSWER 22 OF 22 CAPLUS COPYRIGHT 2003 ACS
1978:15884 CAPLUS
88:15884
Cancerostatic action of the immune-stimulating compound 4-imino-1,3-diazabicyclo-(3,1,0)-hexan-2-one, BM 06 002, (proposed inn **imexon**) on various transplantation tumors
Bicker, U.; Hebold, G.
Boehringer Mannheim G.m.b.H., Mannheim, Fed. Rep. Ger.
IRCS Medical Science: Library Compendium (1977), 5(9), 428
CODEN: IRLCDZ; ISSN: 0305-6651
Journal
English
BM 06002 (I [59643-91-3] (5 mg/kg, i.v.) given to mice had an antitumor activity against Friend virus leukemia, whereas cyclophosphamide (125 mg/kg, i.v.) had only a slight activity. I injected i.v. at 125 mg/kg into mice showed only a slight effect on Ehrlich ascites carcinoma in mice. I given orally to rats at this dose showed a clear cancerostatic effect on Walker carcinosarcoma.

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SCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
SUBSCRIBER PRICE	-14.97	-15.62

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